ORIGINAL RESEARCH

Development of a Predictive Nomogram for Intra-Hospital Mortality in Acute Ischemic Stroke Patients Using LASSO Regression

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Background and Purpose: Ischemic stroke is a leading cause of mortality and disability globally, necessitating accurate prediction of intra-hospital mortality (IHM) for improved patient care. This study aimed to develop a practical nomogram for personalized IHM risk prediction in ischemic stroke patients.

Methods: A retrospective study of 422 ischemic stroke patients (April 2020 - December 2021) from Chongqing Medical University's First Affiliated Hospital was conducted, with patients divided into training (n=295) and validation (n=127) groups. Data on demographics, comorbidities, stroke risk factors, and lab results were collected. Stroke severity was assessed using NIHSS, and stroke types were classified by TOAST criteria. Least absolute shrinkage and selection operator (LASSO) regression was employed for predictor selection and nomogram construction, with evaluation through ROC curves, calibration curves, and decision curve analysis.

Results: LASSO regression and multivariate logistic regression identified four independent IHM predictors: age, admission NIHSS score, chronic obstructive pulmonary disease (COPD) diagnosis, and white blood cell count (WBC). A highly accurate nomogram based on these variables exhibited excellent predictive performance, with AUCs of 0.958 (training) and 0.962 (validation), sensitivities of 93.2% and 95.7%, and specificities of 93.1% and 90.9%, respectively. Calibration curves and decision curve analysis validated its clinical applicability.

Conclusion: Age, admission NIHSS score, COPD history, and WBC were identified as independent IHM predictors in ischemic stroke patients. The developed nomogram demonstrated high predictive accuracy and practical utility for mortality risk estimation. External validation and prospective studies are warranted for further confirmation of its clinical efficacy.

Keywords: ischemic stroke, nomogram, predictors, lasso, intra-hospital mortality

Introduction

Ischemic stroke is one of the primary causes of disability and death among adults worldwide. The 2019 Global Burden of Disease Study reported approximately 7.63 million cases of ischemic stroke globally, with China accounting for 2869 thousand of these cases.[1,2] Notably, strokes constituted 11.6% of global mortality that year, with around 6.55 million people worldwide succumbing to stroke-related causes. Of these, approximately 3.29 million deaths were due to ischemic strokes, accounting for 50.2% of all stroke-related fatalities.[1] It is important to highlight that the majority of these deaths occurred during the acute phase, primarily within hospital settings, a phenomenon known as intra-hospital mortality (IHM).[3] Cardioembolic strokes and atherothrombotic strokes, subtypes of ischemic stroke, are particularly associated

with the highest rates of in-hospital mortality. These subtypes often result in more severe clinical outcomes and have a significantly poorer short-term prognosis compared to other forms of ischemic stroke.[4]

Despite the effectiveness of treatments such as intravenous thrombolysis with recombinant tissue plasminogen activator, mechanical thrombectomy, and care in specialized stroke units, the IHM rate among ischemic stroke patients remains high.[5] This is largely due to the narrow therapeutic window and the risk of severe complications associated with these treatments.[6,7] Additionally, due to significant differences in stroke severity, age, time of admission, medical history, socioeconomic factors, and complications during hospitalization among stroke patients, identifying factors that influence IHM is crucial for providing timely and appropriate care and improving patient outcomes.[8] By identifying individuals at high risk of mortality, they can be prioritized for admission into acute stroke units, thereby enhancing the prognosis for patients with acute ischemic stroke.

Previous research has explored predictors of IHM among ischemic stroke patients, including age, comorbidities, stroke subtypes, and certain laboratory parameters like elevated blood glucose levels and increased white blood cell count (WBC), which may predict IHM rates.[9–11] Additionally, recent studies have found a correlation between the admission shock index and stroke mortality rates.[12]

Although various prognostic scores for acute stroke patients—such as iSCORE, MEWS, PLAN, ASTRAL, and SOAR—have been assessed for their predictive capabilities.[13–17] However, due to variations in study populations and differences in variable selection, a universally accepted stroke mortality prediction score has yet to be established.

The nomogram, an intuitive visual tool, has been widely used to predict long-term mortality rates, stroke-associated infections, malignant brain edema, post-stroke depression, hemorrhagic transformation, and adverse outcomes in different stroke subgroups.[18–22] However, to our knowledge, there is currently no nomogram specifically for predicting the risk of IHM in ischemic stroke patients. Thus, this study aims to develop a simple and reliable clinical tool to predict the risk of IHM in ischemic stroke patients using readily available pre-hospital clinical data and admission laboratory indicators. This tool is intended to provide clinicians with a concise and effective method for assessing risk, thereby facilitating better patient care.

Materials and Methods
Study Design and Participants
This study received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval No.: 2022–115) and was conducted in accordance with the Helsinki Declaration principles. It was a retrospective observational study that included patients with acute ischemic stroke admitted to the Department of Neurology at the First Affiliated Hospital of Chongqing Medical University from April 2020 to December 2021.

The inclusion criteria were as follows: 1) age ≥ 18 years, regardless of gender; 2) availability of all clinical and laboratory data; 3) all cases of stroke meeting the diagnostic criteria for acute ischemic stroke, confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scans as cerebral infarction; 4) obtaining informed consent from patients or their legal guardians. Exclusion criteria included: 1) medical records with missing data; 2) pregnant or lactating patients; 3) patients who declined to participate in the study.

Initially, a total of 545 patients were enrolled. Based on the inclusion and exclusion criteria, 422 patients were finally included. All patients were randomly divided into a training group (n=295) and a validation group (n=127) at a ratio of 7:3 (Figure 1).

Data Collection
We employed standardized data collection forms to retrieve patients' demographic information, pre-admission comorbidities, stroke risk factors, and laboratory test results from the electronic medical record system. This encompassed details such as age, gender, blood pressure, clinical features, diabetes, hypertension, heart disease, among others. Additionally, we documented the initial laboratory test results obtained upon admission, including parameters like complete blood cell count, hemoglobin (Hb) levels, white blood cell count (WBC), mean corpuscular volume (MCV), and other biochemical indicators.
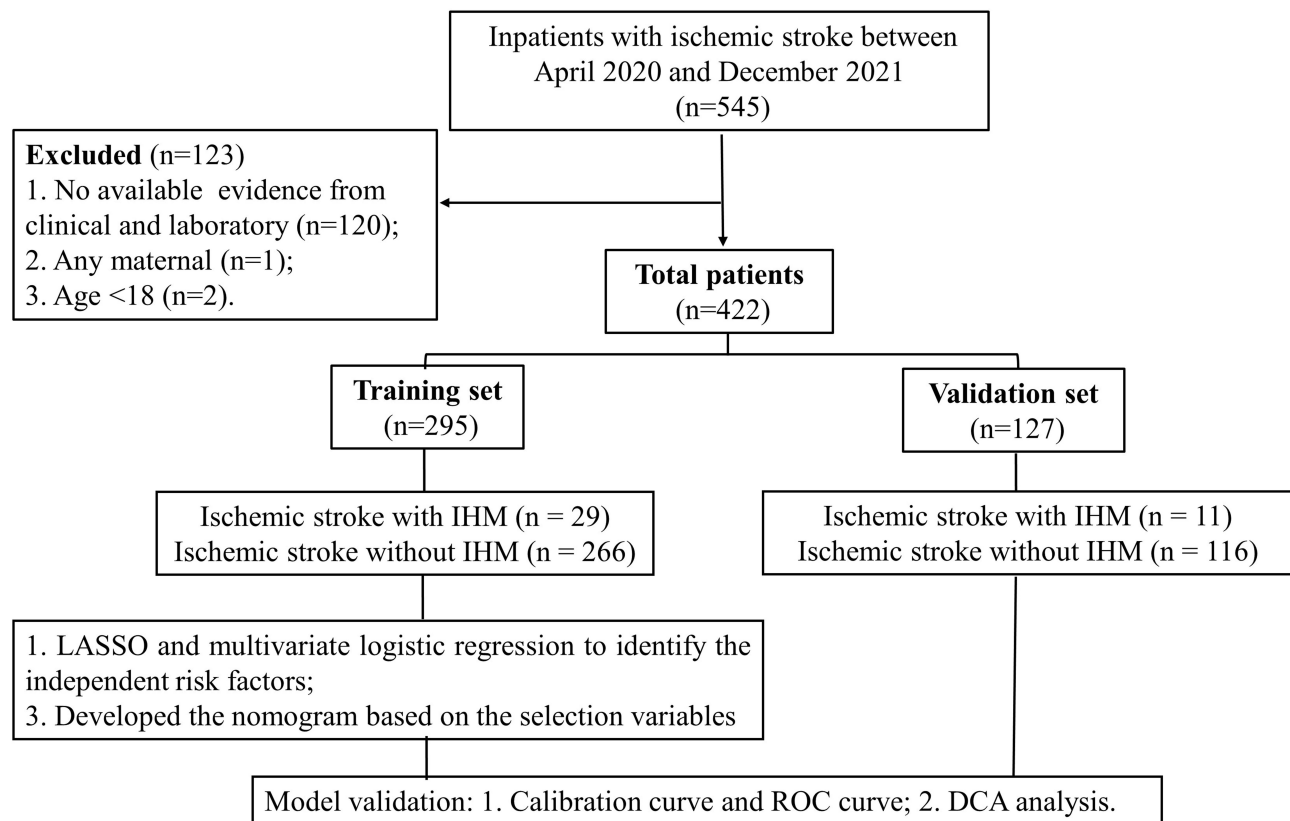
Inpatients with ischemic stroke between
April 2020 and December 2021
(n=545)

Excluded (n=123)
1. No available evidence from
clinical and laboratory (n=120);
2. Any maternal (n=1);
3. Age <18 (n=2).

Total patients
(n=422)

Training set
(n=295)

Validation set
(n=127)

Ischemic stroke with IHM (n = 29)
Ischemic stroke without IHM (n = 266)

Ischemic stroke with IHM (n = 11)
Ischemic stroke without IHM (n = 116)

1. LASSO and multivariate logistic regression to identify the
independent risk factors;
3. Developed the nomogram based on the selection variables

Model validation: 1. Calibration curve and ROC curve; 2. DCA analysis.

Figure 1 Flowchart of participant selection.
Abbreviations: IHM, intra-hospital mortality; ROC, receiver operator characteristic curve; DCA, decision curve analysis.

The severity of the stroke upon admission was assessed using the NIHSS, and stroke subtypes were classified according to the TOAST criteria. All patients received MRI or CT scans within 72 hours of admission.

Additionally, we recorded whether patients died during their hospitalization, and based on this, all patients were divided into two groups: Ischemic stroke with IHM and Ischemic stroke without IHM.

Statistical Analysis

The statistical analysis was performed using SPSS (IBMCorp version 26.0) and R version 4.3.2. Firstly, we conducted a normality test for all continuous variables using the K–S test. The results indicated that none of the included continuous variables followed a normal distribution. Therefore, we described them using the median (interquartile range) and compared the differences between two groups using the Mann–Whitney U-test. For categorical variables, we represented them with numbers (percentages, %) and compared them using either the chi-square test or Fisher's exact test. A significance level of $P < 0.05$ (two-tailed) was considered statistically significant.

Multicollinearity among predictor variables was rigorously evaluated using the Variance Inflation Factor (VIF) and tolerance levels. Only variables exhibiting a VIF less than 5 and a tolerance greater than 0.1 were retained for further analysis, ensuring the stability and interpretability of our regression models. We employed the least absolute shrinkage and selection operator (LASSO) regression technique for data dimensionality reduction and initial predictor selection, effectively addressing multicollinearity and enhancing model parsimony by penalizing the regression coefficients, leading to exclusion of less significant or highly collinear variables. The variables selected via LASSO regression were subsequently analyzed using multivariable logistic regression to construct a predictive model and nomogram for IHM in ischemic stroke patients. This two-step approach ensured that our final model included only the most relevant predictors, free from problematic multicollinearity.

The performance of the developed nomogram was evaluated using the 'rms' package in RStudio. The discriminatory ability of the nomogram was assessed using receiver operating characteristic ROC curves, generated using the "Proc" package in RStudio. Additionally, we performed the Hosmer-Lemeshow test and calibrated the model using calibration curves and P-values. We conducted 1000 bootstrap resamples to obtain more accurate calibration results. Furthermore, we assessed the clinical utility of the nomogram using decision curve analysis (DCA), which calculated the net benefit of the model at different threshold risks using the "rmda" package. All graphics were created using R version 4.3.2.

Results
Study Populations

Between April 2020 and December 2021, a total of 545 ischemic stroke patients were screened. Of these, 123 were excluded due to missing data (n=120), pregnancy (n=1), being under the age of 18 years (n=2), and other reasons. Consequently, 422 subjects were deemed eligible for the final analysis. These subjects were then randomly divided into a training set (n=295) and a validation set (n=127) (refer to Figure 1). The median age was 65 years (56–72 years) for the training set and 67 years (61–75 years) for the validation set.

Table 1 summarizes the demographic and clinical characteristics of the study participants. No significant statistical differences ($P > 0.05$) were observed in baseline characteristics, including demographic factors, clinical features, and predictive factors, between the training and validation sets. This indicates that the random allocation of participants into their respective cohorts was scientifically sound.

Table 1 Baseline Characteristics of Subjects in the Training Set and Validation Set

Variables	Total (n=422)	Training Set (n=295)	Internal Validation Set (n = 127)	P
Age (years)	66.00(57.00,74.00)	65.00(56.00,72.00)	67.00(61.00,75.00)	0.132
BMI (kg/m²)	23.03 (20.96, 25.54)	22.98(20.82,25.04)	23.51(21.78,25.95)	0.111
Ischemic Stroke with IHM (%)	40 (9.48)	29(9.83)	11(8.66)	0.707
LAAS	205 (48.58)	139 (47.12)	66(51.97)	0.361
CEI	138 (32.70)	102 (34.57)	36(28.35)	0.211
SVD	65 (15.40)	43 (14.57)	22(17.32)	0.473
Other	8 (1.90)	6(2.03)	2(1.57)	0.747
Unexplained Type	6 (1.42)	5(1.69)	1(0.79)	0.673
Admission NIHSS score	3.00(1.00,7.75)	3.00(1.00,8.00)	3.00(1.00,8.00)	0.571
Female (%)	227(53.79)	156(52.88)	71(55.91)	0.568
Smoking (%)	204(48.34)	143(48.47)	61(48.03)	0.933
Alcohol Drinks (%)	148(35.07)	99(33.59)	49(38.58)	0.321
History of Diagnosis				
Hypertension Diagnosis (%)	234(55.45)	158(53.55)	76(59.84)	0.234
Diabetes Diagnosis (%)	128(30.33)	88(29.83)	40(31.50)	0.733
Previous Ischemic Stroke or Transient Ischemic Attacks (%)	50(11.85)	34(11.53)	16(12.60)	0.754
Carotid Artery Disease (%)	3(0.71)	2(0.68)	1(0.79)	1.000
Peripheral Arterial Disease (%)	6(1.42)	4(1.36)	2(1.57)	1.000
Intracerebral Hemorrhage (%)	6(1.42)	6(2.03)	0(0.00)	0.185
Depression (%)	1(0.24)	1(0.34)	0(0.00)	1.000
Lipid Diagnosis (%)	5(1.18)	4(1.36)	1(0.79)	1.000
Atrial Fibrillation (%)	22(5.21)	13(4.41)	9(7.09)	0.256
Coronary Heart Disease (%)	38(9.00)	30(10.17)	8(6.30)	0.203
Chronic Heart Disease (%)	14(3.32)	11(3.73)	3(2.36)	0.567
Thyroid Disease (%)	1(0.24)	1(0.34)	0(0.00)	1.000
Gastrointestinal Disorders (%)	5(1.18)	3(1.02)	2(1.57)	0.639
Nephritis, Nephrotic Syndrome and Nephrosis (%)	4(0.95)	3(1.02)	1(0.79)	0.082

(*Continued*)

Table 1 (Continued).

Variables	Total (n=422)	Training Set (n=295)	Internal Validation Set (n = 127)	P
COPD (%)	22(5.21)	15(5.10)	7(5.51)	0.856
Malignant Neoplasms (%)	7(1.66)	7(2.37)	0(0.00)	0.108
Surgery (%)	26(6.16)	17(5.76)	9(7.09)	0.660
Family History	21(4.98)	16(5.42)	5(3.94)	0.631
Hematological Findings				
WBC (10^9/L)	7.28(5.88, 9.53)	7.19(5.73,9.44)	7.50(6.13,9.84)	0.203
RBC (10^{12}/L)	4.60 (4.21,4.96)	4.60(4.21,4.98)	4.62(4.20,4.91)	0.881
PLT(10^9/L)	204.50(168.25,252.00)	203.00(172.00,251.00)	209.00(166.00,257.00)	0.901
Hb (g/L)	138.50(128.00,150.00)	139.00(128.00,151.00)	138.00(128.00,148.00)	0.705
MCV (fl)	92.20(89.40,95.20)	92.20(89.40,95.20)	92.30(89.10,95.20)	0.739
MCHC (g/L)	331.00(322.25,338.00)	331.00(322.00,338.00)	332.00(325.00,338.00)	0.156
HCT (%)	42.00(38.83, 44.88)	42.1 (38.80,45.20)	41.70(39.40,44.40)	0.687
BUN (mmol/L)	5.50(4.60, 6.70)	5.50(4.60,6.60)	5.60(4.70, 6.90)	0.334
Crea (μmol/L)	68.00(57.00,82.00)	68.00(57.00,81.00)	69.00(57.00,86.00)	0.326
ALT (U/L)	26.00(20.00,33.00)	26.00(20.00,33.00)	25.00(20.00,32.00)	0.588
AST (U/L)	25.00(21.00,30.00)	25.00(21.00,31.00)	25.00(21.00,30.00)	0.484
FBS (mmol/l)	5.40(4.90,6.50)	5.40(4.90,6.50)	5.50(4.90,6.50)	0.916
HbA1c (%)	5.70(5.40,6.20)	5.70(5.40,6.20)	5.70(5.40,6.20)	0.804
CRP (mg/mL)	1.06(0.47,3.78)	0.90(0.41,2.82)	1.07(0.57,3.15)	0.055
PCT (ng/mL)	0.03(0.02, 0.05)	0.03(0.02, 0.05)	0.03(0.02, 0.05)	0.499
LDL (mmol/L)	2.59(1.97, 3.19)	2.61 (1.96,3.19)	2.57(2.03,3.19)	0.993
D2 (mg/L FEU)	0.39(0.23, 0.94)	0.37(0.23,0.86)	0.45(0.23,1.07)	0.340
Vitamin B12 (pg/mL)	254.50(193.50,360.38)	252.00(195.00,369.00)	273.00(187.00,353.50)	0.803
Folate (ng/mL)	9.550 (6.425,15.35)	9.50(6.50,15.40)	9.70(5.90,14.80)	0.487
tHcy (μmol/L)	12.40(9.90,15.68)	12.40(9.90,15.50)	12.5 (9.90,16.20)	0.640

Note: Data are presented as median (IQR), numbers, or percentages.
Abbreviations: LAAS, large-artery atherosclerosis; CEI, cardio embolism; SVD, small vessel disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood count; PLT, platelets; Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; BUN, blood urea nitrogen; Crea, creatinine; ALT, alanine transaminase; AST, aspartate transaminase; D2, D-dimer; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; PCT, procalcitonin; LDL, low-density lipoprotein; tHcy, total Homocysteine.

LASSO Regression for Predictive Variable Selection

Figures 2A and B depict the outcomes of utilizing LASSO regression analysis to filter through the clinical and laboratory characteristics of participants in the training set. This analysis identified 14 predictor variables associated with IHM in ischemic stroke, including small vessel disease (SVD), large-artery atherosclerosis (LAAS), the admission NIHSS score, history of previous ischemic stroke or transient ischemic attacks, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, surgical history, age, WBC, blood urea nitrogen (BUN), MCV, low-density lipoprotein cholesterol (LDL), and vitamin B12 levels.

Construction of Predictive Model

The 14 predictor variables identified via LASSO regression were further analyzed using multivariate logistic regression, leading to the identification of four independent risk factors associated with IHM in ischemic stroke: age, admission NIHSS score, history of chronic obstructive pulmonary disease (COPD), and WBC, all significant at P < 0.05, as shown in Table 2. Based on these predictive factors, a nomogram was developed, which is presented in Figure 3.

Validation of Predictive Model

Figures 4A and B demonstrate the nomogram's performance evaluation using area under the ROC (AUC-ROC) curve for both the training and validation sets. The AUC reached 0.958 (95% CI: 0.918–0.997) in the training set, accompanied by a sensitivity of 93.2% and a specificity of 93.1%. In the validation set, the AUC stood at 0.962 (95% CI: 0.898–1.000),
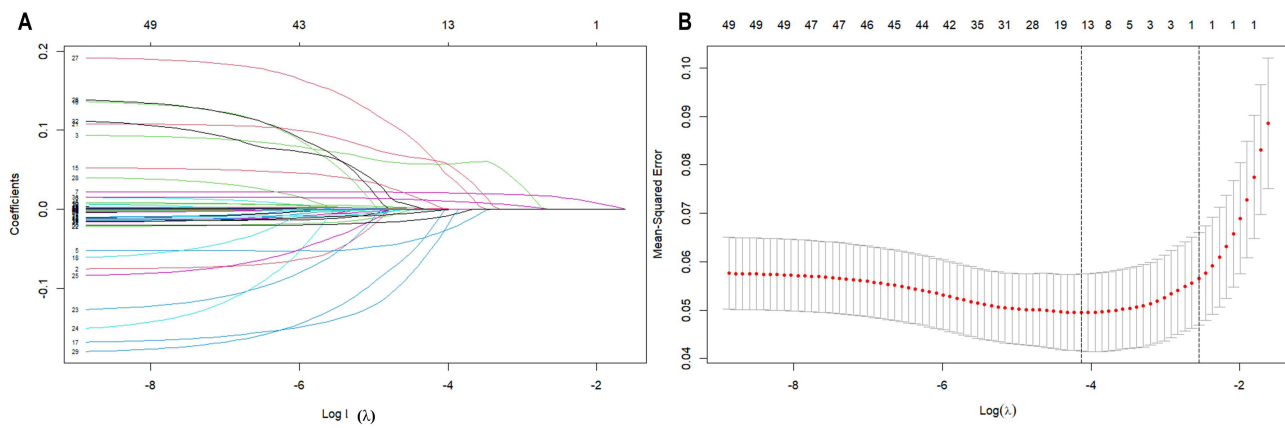
Figure 2 LASSO regression analysis employing tenfold cross-validation to identify predictors of IHM in ischemic stroke. (**A**) This is a coefficient profile plot created based on the log(λ) sequence. The x-axis represents the logarithm of λ, while the y-axis represents the regression coefficients. Each colored solid line in the graph represents a variable. As log(λ) increases, the coefficients of the variables continuously decrease, with some variable coefficients approaching zero; (**B**) represents a 10-fold cross-validation curve for LASSO regression. The x-axis represents the logarithm of λ, and the y-axis represents the mean squared error (MSE). The dashed line on the left side of the graph indicates the λ value (0.01606023) corresponding to the minimum MSE, while the dashed line on the right side indicates the λ value (0.07809452) that is one standard deviation away from the minimum MSE. In this study, the selection of predictors is based on the λ value that is one standard deviation away from the minimum MSE (the right dashed line), where 14 non-zero coefficients were selected.

with a sensitivity of 95.7% and a specificity of 90.9%. Further, Figures 4C and D and Table 3 compare the score differences between the nomogram and individual predictor variables, highlighting that the nomogram consistently outperforms other individual risk prediction indicators in both the training and validation sets. These results underscore the nomogram's robust predictive capability.

The calibration curves indicate that the predicted probabilities of IHM associated with ischemic stroke align closely with the observed integral values in both the training and validation sets ($P > 0.05$). In Figure 5A, we demonstrate the remarkable consistency between the predicted probabilities of IHM for ischemic stroke and the actual observed values in the training set, with a mean absolute deviation (MAD) of 0.079. Similarly, as shown in Figure 5B, the predictions in the validation set accurately reflect the probabilities of IHM for ischemic stroke (MAD = 0.091). Through the evaluation of

Table 2 Multivariate Logistic Regression Analysis of Influencing Factors for Ischemic Stroke with IHM and Without IHM in the Training Set

Variables	β	SE	Multivariate Analysis	
			OR (95% CI)	P-value
Age (years)	0.097	0.040	1.102(1.018,1.192)	**0.016**
LAAS	−1.270	1.261	0.281(0.024,3.326)	0.314
SVD	0.787	1.289	2.196(0.176,27.447)	0.542
Admission NIHSS Score	0.271	0.057	1.311(1.172,1.466)	**<0.001**
History of Previous Ischemic Stroke or Transient Ischemic Attacks (%)	0.619	1.427	1.857(0.113,30.433)	0.664
History of Peripheral Arterial Disease (%)	−5.646	4.661	0.004(0.000,11.290)	0.871
History of Atrial Fibrillation (%)	−0.008	1.454	0.992(0.057,17.149)	0.996
History of COPD (%)	3.358	1.640	8.735(1.154,15.436)	**0.041**
History of surgery (%)	−4.472	4.412	0.011(0.000,65.092)	0.311
WBC (10^9/L)	0.295	0.127	1.343(1.048,1.722)	**0.020**
BUN (mmol/L)	−0.486	0.255	0.615(0.373,1.013)	0.057
MCV (fl)	−0.027	0.061	0.974(0.864,1.097)	0.660
LDL (mmol/L)	−0.887	0.499	0.411(0.155,1.094)	0.075
Vitmian B12 (pg/mL)	0.002	0.002	1.002(0.998,1.006)	0.409

Note: Bold text indicates a statistically significant difference with a *p*-value less than 0.05.
Abbreviations: LAAS, large-artery atherosclerosis; SVD, small vessel disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; BUN, blood urea nitrogen; MCV, mean corpuscular volume; LDL, low-density lipoprotein.
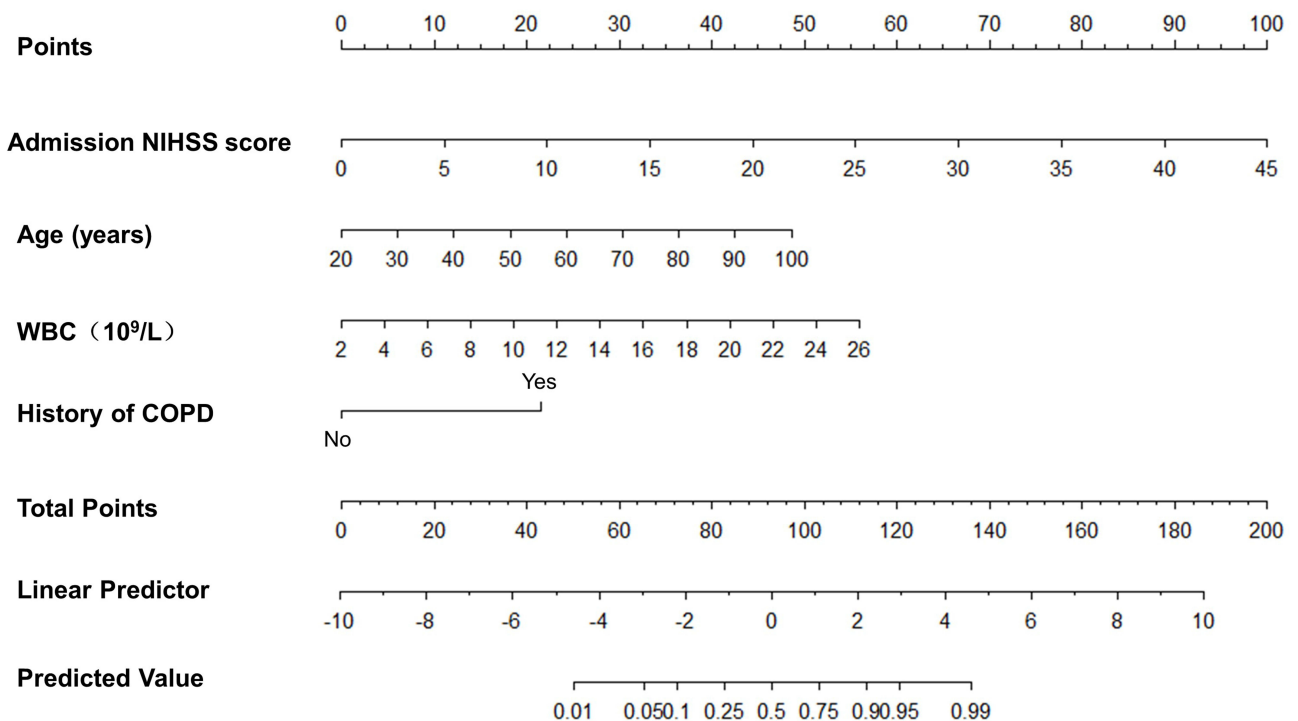
Figure 3 The nomogram for ischemic stroke with IHM. The nomogram assigns scores to each variable, allowing the evaluation of the probability of ischemic stroke with IHM by summing the scores tied to specific patient values. For instance, take a patient admitted for ischemic stroke with an NIHSS score of 20, which corresponds to a score of 48; an age of 70 years, yielding a score of approximately 30; a diagnosis of COPD, adding a score of about 21; and a WBC count of 16, equating to a score of 34. The aggregate of these scores is 133. According to the nomogram's probability graph for ischemic stroke with IHM, this total score suggests an IHM occurrence probability of approximately 95%, classifying the patient within the high-risk category for ischemic stroke with IHM.
Abbreviations: WBC, white blood cell; COPD, chronic obstructive pulmonary disease.

the model's fit using calibration curves, we find a strong correspondence between predicted and actual probabilities, highlighting the robust predictive performance of the model.

As shown in Figures 5C and D, the DCA plots of both the training and validation sets exhibit a clinical net benefit ranging from 5% to 100%, indicating high clinical utility for both models. This suggests that the developed nomogram possesses robust predictive capability.

Discussion

This study developed a user-friendly nomogram for predicting IHM of ischemic stroke patients in neurology wards. We collected general clinical characteristics and initial laboratory test results upon admission from ischemic stroke patients. Using LASSO regression and multivariable logistic regression, we identified independent risk factors including patients' age, admission NIHSS score, history of COPD, and WBC, and constructed the nomogram. Furthermore, after ROC curve, calibration curve, and DCA curve analyses, the nomogram demonstrated good discriminative ability, calibration, and clinical utility. We established a model to predict IHM of ischemic stroke patients, which can be utilized for assessing disease severity, guiding treatment, and improving prognosis.

Ischemic stroke has long been a major cause of disability and mortality among patients. With the aging of the population, the global incidence of ischemic stroke has sharply increased. Of note, in all stroke patients, a considerable proportion succumbs to IHM. Our study found that the overall IHM rate of ischemic stroke patients is 9.8%, consistent with previous research findings.[23–25] Nomograms, as a visualization tool for clinical prediction models, have been widely used in the field of ischemic stroke. For instance, Zhang and colleagues developed a nomogram based on four clinical features (female gender, lymphocyte count, pulmonary infection, and mechanical ventilation) and a nutritional risk score (mNUTRIC score), which reliably predicts the in-hospital mortality rate of acute stroke patients.[26] However, since all patients were from the Neurological Intensive Care Unit and the nutritional risk score was used, this limits its application
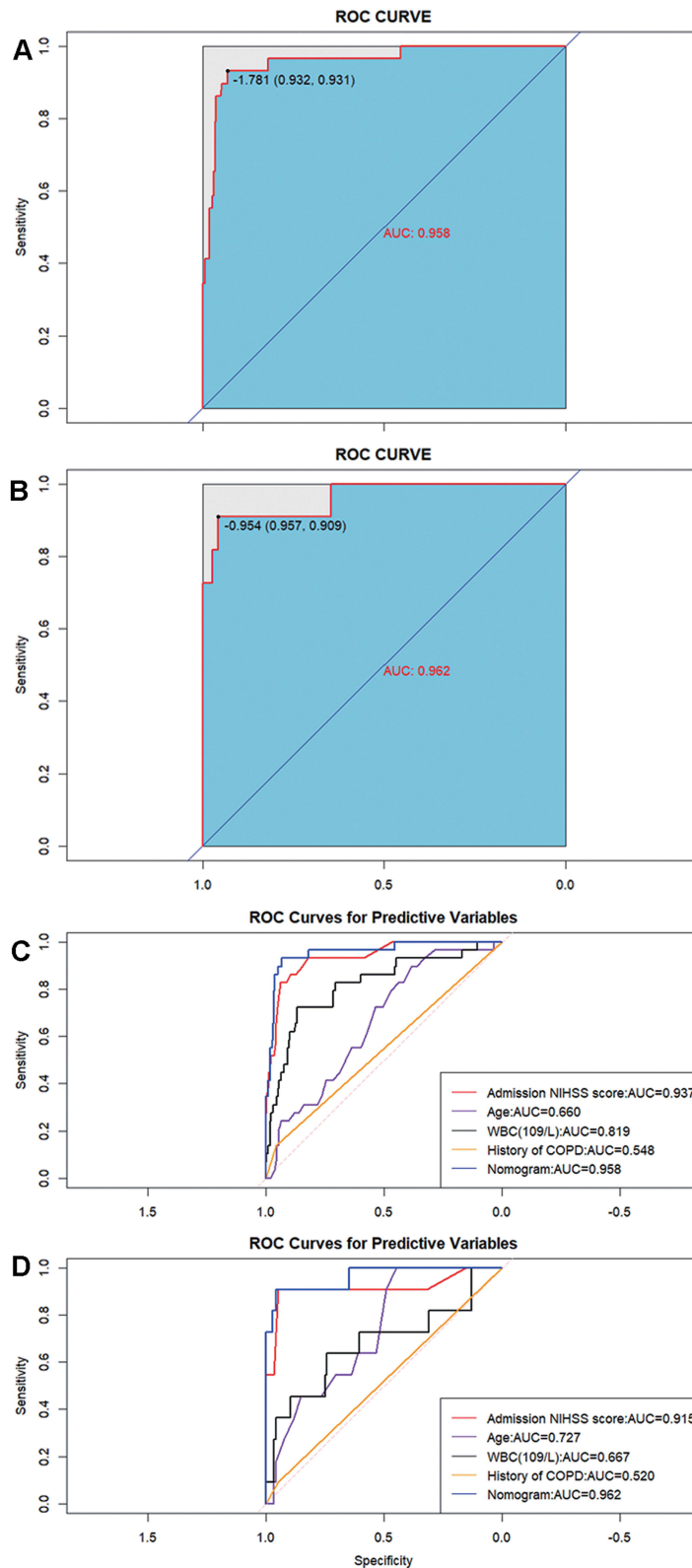
Figure 4 ROC of the nomogram in the training (**A** and **C**) and validation (**B** and **D**) sets.
Abbreviations: WBC, white blood cell; COPD, chronic obstructive pulmonary disease.

Table 3 The Value Evaluation for the Risk Models in Training and Validation Sets

Variables	AUC	95% CI	Specificity	Sensitivity	Positive Predictive Value	Negative Predictive Value	P^
Training Set							
Admission NIHSS score	0.937	0.891–0.983	0.940	0.828	0.600	0.980	0.214
Age (years)	0.660	0.565–0.755	0.383	0.897	0.137	0.971	**0.003**
WBC (10^9/L)	0.819	0.727–0.910	0.868	0.724	0.375	0.966	**0.002**
History of COPD (%)	0.548	0.482–0.613	0.959	0.140	0.267	0.911	**<0.001**
Nomogram	0.958	0.918–0.997	0.932	0.931	0.600	0.992	Reference
Validation set							
Admission NIHSS score	0.915	0.781–1.000	0.948	0.909	0.625	0.991	0.090
Age (years)	0.727	0.595–0.860	0.448	1.000	0.147	1.000	**<0.001**
WBC (10^9/L)	0.677	0.473–0.881	0.741	0.636	0.189	0.956	**0.003**
History of COPD (%)	0.520	0.428–0.611	0.948	0.091	0.143	0.917	**<0.001**
Nomogram	0.962	0.898–1.000	0.957	0.909	0.667	0.991	Reference

Note: ^Comparison in Predictive Power of the Nomogram and other models. Bold text indicates a statistically significant difference with a *p*-value less than 0.05.
Abbreviations: WBC, white blood cell; COPD, chronic obstructive pulmonary disease.

in a broader clinical setting. Additionally, the nomograms developed by Jin et al for predicting the 28-day and 1-year mortality rates of ischemic stroke patients also demonstrated good clinical efficacy.[27,28] In our research, we identified four independent risk factors associated with IHM in ischemic stroke patients: patient age, admission NIHSS score, history of COPD, and WBC. The identification of these factors not only simplifies the assessment process but also shows good potential for clinical application.

This study reaffirms that advanced age is an independent risk factor for IHM in ischemic stroke patients, aligning with findings from previous research.[20] Prior studies have underscored the connection between stroke incidence and aging,
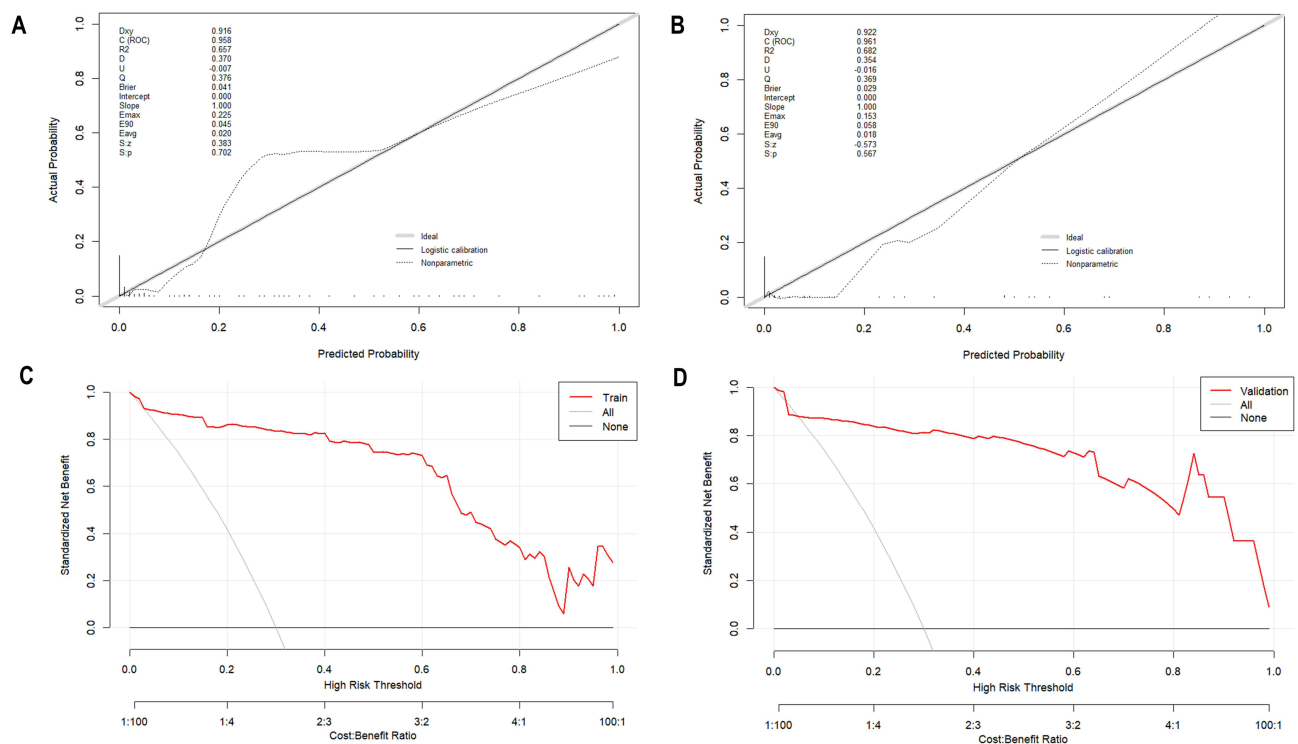

Figure 5 Calibration curve of nomogram for predicting the risk of ischemic stroke with IHM in both the training (**A**) and validation (**B**) sets (All *P*>0.05). Decision curve analysis (DCA) of the nomogram for predicting the risk of acute IS with IHM in the training (**C**) and the validation set (**D**).

noting that between 75% and 89% of strokes occur in individuals aged 65 and older—a proportion that escalates with advancing age.[29] In contrast to younger individuals, who generally exhibit more favorable outcomes, older ischemic stroke patients face higher mortality rates and more severe neurological deficits, thereby underscoring the significance of age as a crucial determinant of IHM.[30–33] This study's findings resonate with this perspective. The link between advanced age and increased risk of mortality post-stroke is supported by several studies that have explored the underlying biological mechanisms. Aging is known to alter the immune microenvironment and the phenotype and function of neutrophils before and after an ischemic stroke event. This results in an elevated production of reactive oxygen species and matrix metalloproteinase-9, which in turn leads to the degradation of the extracellular matrix and the blood-brain barrier, contributing to more extensive infarct volumes.[34,35] Additionally, chronic inflammation, a hallmark of advanced age, can impair endothelial function,[33] further exacerbating neurological damage after a stroke and worsening the prognosis.[36]

The NIHSS score is a widely recognized tool for evaluating stroke severity, extensively used in both clinical practice and research. Research by Adams et al highlighted that higher NIHSS scores at admission correlate with a heightened risk of early mortality in stroke patients,[37] a finding echoed by subsequent research Subsequent studies have further supported this conclusion.[38–40] Aligning with these studies, our research identifies a high NIHSS score upon admission as a significant independent predictor of early IHM in ischemic stroke patients.[41] Hence, our study enhances the existing body of knowledge by emphasizing the importance of initial NIHSS scores at admission as predictors of the risk of early IHM in stroke patients.

COPD is a key risk factor for diseases such as stroke, diabetes, and hypertension.[42] Studies have shown that after experiencing an acute exacerbation, the risk of stroke in COPD patients can be as much as 6.66 times higher than normal.[43] Further research indicates that the overall risk of stroke in COPD patients increases by about 20%,[44] and if COPD conditions worsen, it can significantly raise the mortality rate after a stroke(OR=1.34,95% CI: 1.20–1.52).[45] A study in the United States, after adjusting for multiple influencing factors, found that the positive correlation between COPD and stroke mortality is very clear, whether for overall stroke(OR=1.06, 95% CI: 1.02–1.08) or ischemic stroke (OR=1.08, 95% CI: 1.03–1.13).[46] This increased mortality may be related to gas exchange disorders (such as hypoxemia and hypercapnia) that COPD patients experience during acute exacerbations, as well as an increase in inflammation and oxidative stress.[47,48] Recent research has also revealed that COPD increases the hospital mortality rate of female patients with ischemic stroke by 15%.[49] These findings highlight the importance of implementing effective management and treatment for patients with ischemic stroke who also have COPD.

Previous research has shown that a high WBC significantly increases the hospital mortality rate of patients with ischemic stroke, regardless of other factors such as high blood sugar or low platelet count.[50,51] An increase in WBC in the early stages of ischemic brain injury typically indicates an acute stress response within the body.[52] Such accumulation not only exacerbates the damage to brain tissue caused by vascular occlusion but also disrupts the overall brain structure through the release of a large volume of inflammatory mediators.[53–55] The persistence of these white cells in downstream organs can lead to multi-organ failure, microvascular occlusion, increased blood viscosity, and heightened vascular resistance, aggravating micro-circulatory failure.[56] Furthermore, an abnormal rise in WBC may signal inflammation in other body systems, like pneumonia or urinary tract infections, thus increasing the in-hospital death risk for ischemic stroke patients.[11,57] Supporting this, studies have identified an increase in WBC within 12 hours following an ischemic stroke as a crucial prognostic factor for IHM (OR = 1.27, 95% CI: 1.17–1.39).[58] Our study corroborates these findings, showing a significant association between elevated WBC counts and increased IHM rates (OR = 1.343, 95% CI: 1.048–1.722). Moreover, patients experiencing a sustained rise in WBC for over 48 hours face longer hospital stays, poorer functional outcomes, and a higher likelihood of severe strokes.[59,60]

Our nomogram has several significant advantages. First, it is applicable to all stroke patients aged 18 and above, offering a broad scope of application. The four required indicators are simple and easy to obtain, facilitating external validation and practical application, thus providing an important predictive tool for clinical use. Additionally, the nomogram's intuitive visual design and clear instructions make it user-friendly, easy for clinicians to understand and operate without the need for extensive training. Furthermore, all variables in the model can be seamlessly integrated into existing electronic health record systems, supporting automatic data entry and result generation, significantly reducing the workload for doctors and enhancing work efficiency. Moreover, our nomogram is suitable for clinicians of varying

levels and experience. Through detailed training manuals, online courses, and onsite training, we ensure that all doctors can accurately use this tool. These advantages suggest that our nomogram will be effectively applied and widely promoted in clinical settings.

Our study provides a new method for predicting IHM risk in patients with ischemic stroke, but it also has some limitations. First, as a single-center retrospective study, it inevitably has selection and recall biases and cannot establish causality. Second, due to the small sample size, the statistical significance and generalizability of the study results may be limited. Additionally, due to data collection limitations, this study has not been externally validated, so the generalizability of our findings needs to be further confirmed through future multicenter studies. We recommend that future studies should include common treatments and interventions to further enhance the accuracy of the model. Prospective multicenter research is necessary to assess the practical utility of our proposed nomogram in a broader population and to explore more detailed predictive factors such as the location of cerebral infarcts, age ranges, and the duration of underlying diseases, or to refine the model for specific subgroups of patients with ischemic stroke.[27,28,61,62] Identifying subgroups that may benefit most from the nomogram or have unique prognostic predictors can significantly improve the personalization of stroke management.

Conclusion

In summary, our study identified independent risk factors for IHM among neurology inpatients with ischemic stroke: patients' age, admission NIHSS score, history of COPD, and WBC count. The nomogram developed from these key variables demonstrated excellent predictive performance and clinical utility in assessing the risk of IHM for patients with ischemic stroke. Nevertheless, further external validation and prospective studies are required to confirm the effectiveness of this nomogram.

Abbreviation

IHM, intra-hospital mortality; LASSO, Least Absolute Shrinkage and Selection Operator; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; CT, computed tomography; MRI, magnetic resonance imaging; Hb, hemoglobin; MCV, mean corpuscular volume; VIF, Variance Inflation Factor; DCA, decision curve analysis; SVD, small vessel disease; LAAS, large-artery atherosclerosis; BUN, blood urea nitrogen; LDL, low-density lipoprotein cholesterol; AUC-ROC, area under the ROC; MAD, mean absolute deviation.

Data Sharing Statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

Approval was obtained from institutional review board at the First Affiliated Hospital of Chongqing medical University, Chongqing, China, and the need for informed consent was waived according to the policy (ethic approval code: 2022–115). As the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University did not require patient consent for the review of medical records for this study, all patient data were handled with strict confidentiality. No identifying information has been included in any part of the manuscript.

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Author Contributions

All authors made significant contributions to the conception and design of the study, commented on earlier versions of the manuscript, and read and approved the final manuscript. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work, ensuring the integrity of its content.

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Disclosure

The authors declared that they have no competing interests in this work.

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